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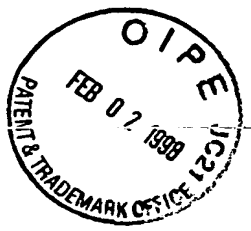
Date: January 28, 1998 By: Gerald F. Swiss



Patent
Attorney's Docket No. 010055-134

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
SIMON BURTON, et al.	Group Art Unit: 1808
Application No.: 08/468,610	Examiner: J. Weber, Ph.D.
Filed: June 6, 1995	
For: CHROMATOGRAPHIC RESINS AND METHODS FOR USING SAME	

REPLY BRIEF

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Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Reply Brief is submitted pursuant to the provisions of 37 C.F.R. §1.193(b)(1) and is in response to the Examiner's Answer mailed on November 28, 1997. This Reply Brief is being submitted on or before its due date of January 28, 1998.

Initially, for the sake of completeness, this appeal is directed to the final rejection of Claims 1-5 and 7-23 under 35 USC § 103 as being unpatentable over Sasaki, et al., *J. Biochem.*, 86:1537-1548 (1979) ("Sasaki '79") or Sasaki, et al., *J. Biochem.*, 91:1551-1561 (1982) (hereinafter "Sasaki '82") in view of Kasche, et al., *J. Chromatogr.*, 510:149-154 (1990) (hereinafter "Kasche"), Teichberg, *J. Chromatogr.*, 510:49-57 (1990) (hereinafter "Teichberg") and Jost, et al., *Biochem. Biophys. Acta*, 362:75-82 (1974) (hereinafter "Jost"). These references were discussed in detail in both Appellants' Brief and the Examiner's Answer and familiarity with these discussions is assumed herein.

Response to Grounds of Rejection

Returning to the Examiner's Answer, the primary emphasis in the Grounds of Rejection section of this Answer are methods described in Sasaki '79 for binding enzymes to a non-charged carboxylate resin followed by a pH increase in order to induce ionic charge (due to carboxylate anions) on the resin which concurrently results in elution of the enzyme from the resin. These methods were characterized in a cartoon in Figure 5 of Sasaki ('82) which is described in detail in the Examiner's Answer.

This argument fails, however, to account for the fact that the appealed claims are *composition* claims and, hence, patentability is premised upon the issue of motivation to prepare these compositions with a reasonable expectation of success. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). For the sake of clarity, such compositions are resin/protein complexes wherein the resin is characterized as being electrostatically uncharged at the pH of protein absorption which, in the claims, is a pH of from 5 to 9. For the reasons noted below and in Appellant's Appeal Brief, nothing in any of the cited references teaches or suggests a resin-protein complex according to these composition claims wherein the resin is uncharged at a pH of from 5-9. For example, according to both Sasaki references, the carboxyl groups of Sasaki's resin (Sasaki '79 or Sasaki '82) are charged at a pH above 4.5 and, hence, the explicit teachings of these references cannot meet the limitations of these compositions claims.

This argument still further fails to account for the fact that neither Sasaki reference teaches or suggests *any* functional groups which would be uncharged at pH 5 to 9, which, as above, is the pH of binding as set forth in the claims on appeal. In contrast, Appellants' specification provides ample disclosure of such suitable groups at, for example, Table 1 at page 23 of Appellants' specification. This explicit failure of both Sasaki references is implicitly acknowledged in the Answer by the Examiner's need to provide his own example of an amine functional group at page 6 of the Answer to illustrate his point. However, such an amine functional group is not disclosed in either

Sasaki reference and the Examiner's exemplification can not and should not be construed as prior art.

At best, the Sasaki ('82) reference discloses the possibility of absorbents carrying alkaline groups instead of carboxyl groups although, as described by Sasaki ('82), the "relationship to pH would be opposite". Such an opposite relationship suggests to the skilled artisan an alkaline pH as far removed from neutrality (pH 7) as the Amberlite resins described by Sasaki ('82). Since Sasaki's Amberlite resins are reported to dissociate at pH 4.5, opposite alkaline charges would dissociate at pH 9.5 which is also outside the range claimed by Appellants.[1]

The Examiner's Answer's reliance on the secondary references fails to cure this deficiency in the Sasaki references because none of these references teach or suggest the use of uncharged resins in binding proteins at a pH of 5 to 9 thereby forming a resin/protein complex of the claimed invention.

Specifically and as noted in Appellants' Brief, the Kasche reference fails to disclose any resin/protein complex wherein the resin is electrostatically uncharged when binding the protein. While the Examiner Answer refers to Figure 2 of Kasche as showing that:

> "at pH values of about 9 and above, the resin is said to bind protein by hydrophobic interactions".

this statement is not found anywhere in Figure 2 of Kasche. All that is recited in Figure 2 is the legend "Protein adsorption by hydrophobic interaction" placed above the pH range of ~ 6.5 to ~ 10. However, as shown in the Appeal Brief, Kasche's resin carries a

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[1] The acidic pH of 4.5 is 2.5 units removed from a neutral pH of 7 and, accordingly, a basic pH equally removed from neutrality would require a pH of 9.5.

significant electrostatic charge at a pH of 7.5 which is recognized by Kasche's statement in the bridging sentence between pages 152 and 153 that:

> "...hydrophobic interactions cause the adsorption, and ... charge-charge repulsions on the support limit the adsorption capacity".

Clearly, Kasche recognizes that his supports carry charge at the pH of absorption. Moreover, Kasche does not teach or suggest binding proteins to uncharged resins in the range of pH 5 to 9. Accordingly, this reference cannot cure the deficiencies of both Sasaki references.

The Examiner's Answer further states that Kasche extends the method of Sasaki to basic resins. This, however, is simply not true. Sasaki requires binding at a pH where the resin is uncharged whereas Kasche, as shown above, employs at least a partially charged resin. The mechanism employed by Kasche to effect protein binding is necessarily different from those of Sasaki and, accordingly, no motivation can exist to combine the teachings of Kasche with those of Sasaki.

The Examiner's Answer concludes, without providing any literature support, that:

> "...the teachings of Kasche et al. confirm that the pH regime where hydrophobic ionic chromatography may be performed is not limited to pH values where the resin is totally uncharged."

However, since Kasche only demonstrates protein binding to partially charged resins in the range of pH 5-9, any correlation made by the Examiner to protein binding to uncharged resins in this pH range is simply not provided by this reference. Kasche simply does not disclose any resin/protein complexes as per this invention.

As to Tiechberg, the clear teachings of this reference are found at page 54, second full paragraph thereof, where it is stated that:

> "...the specific interactions ... which allow the selective retention of the protein on the affinity matrix...involve not only the strictly specific non-covalent binding of the protein to the immobilized ligand but also the less specific (...ionic) interactions either with the spacer arm ... or *with the charged residues on the matrix*. (emphasis added)

Clearly then, Tiechberg purposely employs a charged matrix when binding the protein which teachings are in contrast to the specific recitation of the claimed invention and there is no correlation in Tiechberg to protein binding to uncharged resins in pH range 5-9. Tiechberg simply does not disclose any resin/protein complexes as per this invention and, accordingly, Tiechberg cannot cure the deficiencies of the Sasaki references.

As to Jost, this reference also discloses the necessity of charged groups (i.e., positively charged groups) in the resins described therein to effect protein recovery. Specifically, Jost compares resins conventionally charged at physiological pH (i.e., CNBr activated agarose derivatized with alkyl- and arylamines) versus resins which apparently are uncharged at physiological pH but having one or two dissociation ranges (agarose derivatized with alkyl or aryl hydrazides). Jost states at page 75 (column 2) that:

> "The experiments presented in this paper describe the adsorption of ovalbumin, α-lactalbumin, and leucine aminopeptidase (EC 3.4.1.1) to alkyl- and arylamino-agaroses and demonstrate the abolishment of such binding in structurally closely related uncharged agarose derivatives, prepared from the corresponding alkyl or aryl hydrazides."

The only protein which bound to the uncharged agarose derivatives of Jost was bovine serum albumin (BSA) which Jost recites as being "bound almost irreversibly" to this resin. In point of fact, Jost describes that attempted "[d]esorption [of the BSA] with 1 M

NaCl was unsuccessful". See, for example, the first five lines under Table I of Jost. However, Jost describes that the use of positively charged resin permits binding and recovery of BSA. See, e.g., Table 1 of Jost. Accordingly, Jost teaches that in the absence of charged groups on the resin, two proteins did not bind to the resin and a third (BSA) bound apparently irreversibly to the resin thus preventing recovery of the BSA. As is apparent, irreversible binding in this third resin does not lend itself to protein desorption from the resin.

This section of the Examiner's Answer then concludes that:

> "The selection of a resin from among well-known chromatography resins for use in hydrophobic ionic chromatography where the resin is uncharged in the range of pH of 5-9 involves nothing more than routine experimentation..."

This conclusion is simply not germane to the issues at hand. Appellants' claims are not directed to resins *per se* but rather are composition claims directed to resin/protein complexes. That is to say that the claimed composition comprises both an uncharged resin in the pH range of 5 to 9 and a protein complexing therewith. Nothing in any of the cited references teach or suggest such a complex and there is simply no motivation provided by these references to bind a protein to an uncharged resin in the pH range of 5-9 to arrive at Appellants' claimed compositions. Accordingly, whether an uncharged resin can be prepared by routine experimentation is simply immaterial and should be disregarded.

Response to Examiner's Response to Arguments

The Examiner's Answer concluded with a section entitled "Response to argument" wherein the Examiner purports to rebut Appellants' arguments as set forth in the Appeal Brief. To the extent not addressed previously, Appellants wish to note the following:

1. In the first full paragraph at page 11 of the Examiner's Answer it is stated that:

> "The elution of protein from the matrix as the pH is changed will be intermediate in pH regions where a partial charge is available. This will be in a pH region near the dissociation constant for the functional group on the matrix and can roughly be approximated by the Henderson-Hasselbach equation for acid dissociation."

This statement, is without foundation in the Sasaki references and is otherwise an unsupported allegation by the Examiner and, in fact, is inconsistent with the express teachings of Sasaki which, at page 1557, state that the protein glucose oxidase from *Aspergillus niger* was bound to the Amberlite resin at pH 4.5 and was eluted from this resin at a pH centered at 4.8. If as Sasaki alleges, the resin is uncharged at pH 4.5, the adjustment to pH 4.8 would involve only partial ionization of the resin. Accordingly, the Examiner's conclusion that intermediate elution of a protein correlates with the extent of partial charge on the resin is inconsistent with these results.

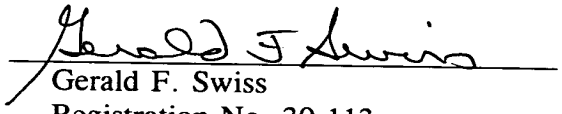
2. In the second full paragraph at page 11 of the Examiner's Answer, it is stated that "at the isoelectric point the protein is uncharged". This statement is also in error. The isoelectric point is defined to be the pH where there are equal number of positive charges and negative charges such that the protein is electrostatically neutral. In contrast, an uncharged material is one which lacks any charge positive or negative on the resin.

In summary, Appellants maintain that the rejection of Claims 1-5 and 7-23 under 35 U.S.C. 103 over Sasaki '79 or Sasaki '82 in view of Kasche, Teichberg, and Jost is in error.

A Request for Oral Hearing is enclosed herewith. Accordingly, notification of the date for Oral Hearing is earnestly solicited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 

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